

02911.000600.



PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)
: Examiner: San Ming R. Hui
OLUWOLE T. ALOBA ET AL.)
: Group Art Unit: 1617
Application No.: 10/023,748)
:
Filed: December 21, 2001)
:
For: ORAL PHARMACEUTICAL)
PRODUCTS CONTAINING 17 β -)
ESTRADIOL-3-LOWER)
ALKANOATE, METHOD OF)
ADMINISTERING THE SAME AND)
PROCESS OF PREPARATION :

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

Tina M. deVries, declares and says that:

1. I am the Vice President of Pharmaceuticals at Galen Holdings, PLC and have been in this position since November 2000. Prior to this, I was the Senior Director of Research and Development of Pharmaceuticals at Warner-Chilcott, which was eventually acquired by Galen Holdings.

2. I graduated from The Ohio State University Graduate School in 1989, with a Doctor of Philosophy in Pharmaceuticals and Pharmaceutical Chemistry.

3. I am one of the named inventors of the above-identified United States Patent Application.

3

4. I am aware that the Examiner has rejected claims 1-3, 5, 10, and 11 under 35 U.S.C. 103(a) as being allegedly unpatentable over U.S. Patent No. 3,478,070 (Stein et al.).

5. I have reviewed the Stein et al. patent and understand it to be a general disclosure for preparing 3-acylated derivatives of d-estradiol. I do not believe that Stein et al. recognized the significant improvement in the relative bioavailability of estradiol found when 17 β -estradiol-3-acetate is administered in an oral preparation. In fact, Stein et al. does not even disclose a preparation containing 17 β -estradiol-3-acetate.

6. This is exemplified in the specification of the application in Example 3, which details a study comparing the bioavailability of 17 β -estradiol-3-acetate to 17 β -estradiol. Each participant received (1) one tablet of 1.152 mg 17 β -estradiol-3-acetate (equivalent to 1 mg of 17 β -estradiol), and (2) one tablet of 1 mg micronized 17 β -estradiol (Estrace® Tablets). Treatments were orally administered, with a one-week washout period between treatments.

7. Nine healthy postmenopausal women participated in the study. All participants were Caucasian. The median age was 57 (47-70) years old, with a median weight of 68.5 (55.0-89.0) kg, and a median height of 156 (149-165) cm. Data from eight of the participants was evaluable.

8. Blood samples were collected serially from each participant about 48 hours before and up to 48 hours after receiving the treatment. The blood samples were analyzed for estradiol concentration by a validated GC/MS assay with a lower limit quantitation of 5 pg/mL.

9. Based upon a preliminary evaluation of the data, the improvement in bioavailability of 17 β -estradiol-3-acetate over 17 β -estradiol was reported to be 15%.

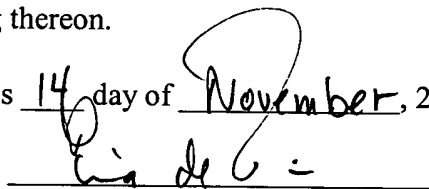
10. Upon a more comprehensive analysis of the data, however, the

improvement in bioavailability was determined to be 19%, rather than 15%. The difference in assessment of bioavailability is attributed to applying a baseline correction to the analytical results. The baseline correction factors into consideration the particular participant's baseline value, i.e., concentration of estradiol in the bloodstream.

11. In my opinion, the result obtained from the comprehensive analysis of the data of Example 3 reflects more accurately, the improvement in bioavailability of the invention, i.e., 17 β -estradiol-3-acetate over 17 β -estradiol. However, it should be understood that even a 15% improvement in bioavailability over 17 β -estradiol would be substantial and unexpected.

12. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Subscribed this 14 day of November, 2003.

A handwritten signature in dark ink, appearing to read "Tina deVries", is written over a horizontal line.

Tina deVries, Ph.D